KRAS and BRAF Mutation Analysis in Metastatic Colorectal Cancer

Policy # 00233
Original Effective Date: 12/17/2008
Current Effective Date: 12/18/2013

Applies to all products administered or underwritten by Blue Cross and Blue Shield of Louisiana and its subsidiary, HMO Louisiana, Inc. (collectively referred to as the “Company”), unless otherwise provided in the applicable contract. Medical technology is constantly evolving, and we reserve the right to review and update Medical Policy periodically.

When Services Are Eligible for Coverage
Coverage for eligible medical treatments or procedures, drugs, devices or biological products may be provided only if:

- Benefits are available in the member’s contract/certificate, and
- Medical necessity criteria and guidelines are met.

Based on review of available data, the Company may consider KRAS mutation analysis to predict nonresponse to anti-epidermal growth factor receptor (EGFR) monoclonal antibodies cetuximab and panitumumab in the treatment of metastatic colorectal cancer to be eligible for coverage.

81210 BRAF (v-raf murine sarcoma viral oncogene homolog B1) (eg, colon cancer), gene analysis, V600E variant

81275 KRAS (v-Ki-ras2 Kirsten rat sarcoma viral oncogene) (eg, carcinoma) gene analysis, variants in codons 12 and 13

When Services Are Considered Investigational
Coverage is not available for investigational medical treatments or procedures, drugs, devices or biological products.

Based on review of available data, the Company considers BRAF mutation analysis to predict nonresponse to anti-EGFR monoclonal antibodies cetuximab and panitumumab in the treatment of metastatic colorectal cancer to be investigational.*

Background/Overview
Cetuximab (Erbitux®, ImClone Systems) and panitumumab (Vectibix®, Amgen) are monoclonal antibodies that bind to the epidermal growth factor receptor (EGFR), preventing intrinsic ligand binding and activation of downstream signaling pathways vital for cancer cell proliferation, invasion, metastasis, and stimulation of neoangiogenesis.

The RAS-RAF-MAP kinase pathway is activated in the EGFR cascade. RAS proteins are G-proteins that cycle between active (RAS-GTP) and inactive (RAS-GDP) forms, in response to stimulation from a cell surface receptor such as EGFR, and act as a binary switch between the cell surface EGFR and downstream signaling pathways. The KRAS gene can harbor oncogenic mutations that result in a constitutively activated protein, independent of EGFR ligand binding, rendering antibodies to the upstream EGFR ineffective. KRAS mutations are found in approximately 30–50% of colorectal cancer tumors and are common in other tumor types. BRAF encodes a protein kinase and is involved in intracellular signaling and...
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cell growth and is a principal downstream effector of KRAS. BRAF mutations occur in less than 10–15% of colorectal cancers and appear to be a marker of poor prognosis.

Cetuximab and panitumumab are approved in the treatment of metastatic colorectal cancer in the refractory disease setting, and ongoing studies are investigating the use of these EGFR inhibitors as monotherapy and as part of combination therapy in first, second, and subsequent lines of therapy. It has been shown that patients with a KRAS mutant tumor do not respond to cetuximab or panitumumab. However, there are still patients with KRAS wild-type tumors that do not respond to these agents, suggesting that other factors, such as alterations in other EGFR effectors could drive resistance to anti-EGFR therapy, and therefore, BRAF mutations are now increasingly being investigated in metastatic colorectal cancer. KRAS and BRAF mutations are considered to be mutually exclusive.

This policy summarizes the evidence for using tumor cell KRAS and BRAF mutational status as a predictor of nonresponse to EGFR-targeted therapy with monoclonal antibodies cetuximab and panitumumab in patients with metastatic colorectal cancer.

FDA or Other Governmental Regulatory Approval

U.S. Food and Drug Administration (FDA)
KRAS and BRAF mutation analyses using PCR methodology are commercially available as laboratory-developed tests. Such tests are regulated under the Clinical Laboratory Improvement Amendments (CLIA). Premarket approval from the U.S. FDA is not required when the assay is performed in a laboratory that is licensed by CLIA for high-complexity testing.

Rationale/Source

KRAS
This policy is based, in part, on a 2008 TEC Assessment.

Randomized, controlled trials (RCTs) have performed nonconcurrent subgroup analyses of the efficacy of EGFR inhibitors in patients with wild-type versus mutated KRAS in metastatic colorectal cancer. The data from these trials have consistently shown a lack of clinical response to cetuximab and panitumumab in patients with mutated KRAS, with tumor response and prolongation of progression-free survival (PFS) observed only in wild-type KRAS patients.

Amado et al. performed a subgroup analysis of KRAS tumor mutations in a patient population that had been previously randomly assigned to panitumumab versus best supportive care as third-line therapy for chemotherapy-refractory metastatic colorectal cancer. The original study was designed as a multicenter, RCT but was not blinded because of expected skin toxicity related to panitumumab administration. Patients were randomly assigned 1:1 to receive panitumumab or best supportive care. Random assignment was stratified by Eastern Cooperative Oncology Group (ECOG) performance status (0 or 1 vs. 2) and geographic region. Crossover from best supportive care to the panitumumab arm was allowed in patients who experienced disease progression. Of the 232 patients originally assigned to best supportive care alone, 176 crossed over to the panitumumab arm, at a median time to crossover of 7 weeks (range: 6.6–7.3).
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Of the 463 patients in the original study, 427 (92%) were included in the KRAS subgroup mutation analysis. A central laboratory performed the KRAS mutational analysis in a blinded fashion, using formalin-fixed, paraffin-embedded (FFPE) tumor sections and a validated KRAS mutation kit (DxS Ltd, Manchester, U.K.) that identifies seven somatic mutations located in codons 12 and 13 using real-time PCR. KRAS mutation status could not be determined in 36 patients because tumor samples were not available or there was insufficient or poor quality DNA. Forty-three percent of the KRAS-evaluable patients had KRAS-mutated tumors, with similar distribution of KRAS mutation types between treatment arms.

Patient demographics and baseline characteristics were balanced between the wild-type (WT) and mutated groups (MT) for panitumumab versus best supportive care including patient age, sex, and ECOG performance status. The interaction between mutational status and PFS was examined, controlling for randomization factors. PFS and tumor response rate was assessed radiographically every 4 to 8 weeks until disease progression using Response Evaluation Criteria in Solid Tumors (RECIST) criteria by blinded, central review. In the KRAS-assessable population, 20% of patients had a treatment-related grade 3 or 4 adverse event. As shown in Table 1, the relative effect of panitumumab on PFS was significantly greater among patients with WT KRAS, compared with patients with MT KRAS in whom no benefit from panitumumab was observed. No responders to panitumumab were identified in the MT group, indicating a 100% positive predictive value for nonresponse in the mutant group.

Table 1. KRAS Status and Efficacy of Panitumumab as Monotherapy in the Treatment of Chemotherapy-Refractory Metastatic Colorectal Cancer

<table>
<thead>
<tr>
<th>Total n=427</th>
<th>KRAS WT</th>
<th>KRAS MT</th>
</tr>
</thead>
<tbody>
<tr>
<td>WT : MT 243 (57%):184 (43%)</td>
<td>P n=124</td>
<td>BSC n=119</td>
</tr>
<tr>
<td>mPFS</td>
<td>12.3 weeks 7.3 weeks (HR 0.45; 95% CI: 0.34–0.59)</td>
<td>7.4 weeks 7.3 weeks (HR 0.99; 95% CI: 0.73–1.36)</td>
</tr>
<tr>
<td>Response rate</td>
<td>17%</td>
<td>0%</td>
</tr>
</tbody>
</table>

WT: wild type; MT: mutated; P: panitumumab; BSC: best supportive care; mPFS: median progression-free survival; HR: hazard ratio; CI: confidence interval

Given the crossover design of the study and the fact that the majority of best supportive care (BSC) patients crossed over to the panitumumab arm early in the trial, conclusions of the effect of KRAS mutational status on PFS and tumor response rate endpoints are limited. However, of the 168 BSC patients that crossed over to panitumumab after disease progression (119 with WT and 77 with MT KRAS), PFS was significantly longer among patients with WT KRAS (mPFS 16.4 weeks for WT vs. 7.9 weeks for MT; HR 0.32; 95% CI: 0.22–0.45).
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After completion of the CRYSTAL trial, in which 1,198 patients with metastatic colorectal cancer were randomly assigned to receive either cetuximab (C) in combination with folinic acid [leucovorin], 5-FU, and irinotecan (FOLFIRI) or FOLFIRI alone for first-line treatment, a subgroup analysis of response rate and PFS according to KRAS mutational status was performed. The original trial design consisted of a central stratified permuted block randomization procedure with geographic regions and ECOG performance status as randomization strata. Two interim assessments of safety data were conducted by an independent data safety monitoring board (DSMB).

Of the original 1,198 patients, 540 had KRAS-evaluable, archival material. KRAS testing was performed from genomic DNA isolated from archived FFPE tissue, using quantitative PCR to detect the KRAS mutation status of codons 12 and 13. It is not stated whether the KRAS mutation analysis was performed blinded; however, the data available are from a video/slide presentation only. KRAS mutations were present in 192 patients (35.6%). No differences were found in patient demographics or baseline characteristics between the MT and WT populations, including age, sex, ECOG performance status, involved disease sites, and liver-limited disease. PFS and tumor response rate were assessed by a blinded, independent review committee by CT scan every eight weeks. A multivariate analysis performed for PFS according to patient characteristics showed a trend for PFS favoring the C plus FOLFIRI combination. The patients with WT KRAS who received C with FOLFIRI showed a statistically significant improvement in median PFS and tumor response rate, whereas the KRAS mutant population did not, as summarized in Table 2.

Table 2. KRAS Status and Efficacy in the First-Line Therapy of Metastatic Colorectal Cancer treated with FOLFIRI with or without Cetuximab (the CRYSTAL Trial; 4)

<table>
<thead>
<tr>
<th></th>
<th>ITT*</th>
<th>KRAS WT n=348** (64.4%)</th>
<th>KRAS MT n=192** (35.6%)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>C + F</td>
<td>F</td>
<td>C + F</td>
</tr>
<tr>
<td>N</td>
<td>599</td>
<td>599</td>
<td>172</td>
</tr>
<tr>
<td>Response rate (%)</td>
<td>46.9 (95% CI: 42.9-51.0)</td>
<td>38.7 (95% CI: 34.8-42.8)</td>
<td>59.3 (95% CI: 51.6-66.7%)</td>
</tr>
<tr>
<td>p value</td>
<td>0.0025</td>
<td>0.46</td>
<td></td>
</tr>
<tr>
<td>mPFS (months)***</td>
<td>8.9</td>
<td>8.0</td>
<td>9.9 8.7 (HR 0.68; p=0.017)</td>
</tr>
</tbody>
</table>

*ITT(intent to treat) in the original CRYSTAL trial assessing C+F versus F alone as first-line therapy for metastatic colorectal cancer.
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**540 patients had available archival pathology material for the KRAS mutation subset analysis.**

***Confidence intervals for mPFS were not provided in the presentation slides.

C: cetuximab; F: FOLFIRI; WT: wild type; MT: mutated; mPFS: median progression-free survival; HR: hazard ratio.

In a third trial, the randomized, Phase II OPUS trial, the ITT population consisted of 337 patients randomly assigned to C and folinic acid [leucovorin], 5-FU, oxaliplatin (FOLFOX) versus FOLFOX alone in the first-line treatment of metastatic colorectal cancer. A 10% higher response rate (assessed by independent reviewers) was observed in the population treated with C, but no difference in PFS was seen between the two groups. The researchers then re-evaluated the efficacy in the two treatment arms with consideration of KRAS mutational status of the patients’ tumors. Of the original ITT population, 233 subjects had evaluable material for KRAS testing, and 99 (42%) were KRAS mutant. There was no difference in demographics or baseline characteristics between the WT and MT groups, including patient age, sex, ECOG performance status, involved disease sites, and liver-limited disease. The study showed that the addition of C to FOLFOX resulted in a significant improvement in response rate and PFS only in the WT KRAS group. The study findings are summarized in Table 3.

**Table 3. KRAS Status and Efficacy in the First-Line Therapy of Metastatic Colorectal Cancer Treated with FOLFOX with or without Cetuximab (OPUS Study, 5)**

<table>
<thead>
<tr>
<th></th>
<th>KRAS WT n=134 (58%)</th>
<th></th>
<th>KRAS MT n=99 (42%)</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>C + Fx</td>
<td>Fx</td>
<td>C + Fx</td>
<td>Fx</td>
</tr>
<tr>
<td>n (KRAS evaluable)</td>
<td>61</td>
<td>73</td>
<td>52</td>
<td>47</td>
</tr>
<tr>
<td>Response rate (%)</td>
<td>60.7% (95% CI: 47.3-72.9%)</td>
<td>37.0% (95% CI: 26.0-49.1%)</td>
<td>32.7% (95% CI: 20.3-47.1)</td>
<td>48.9% (95% CI: 34.1-63.9%)</td>
</tr>
<tr>
<td>p value</td>
<td>p=0.011</td>
<td></td>
<td>p=0.106</td>
<td></td>
</tr>
<tr>
<td>Odds ratio</td>
<td>2.54 (95% CI: 1.24-5.23)</td>
<td></td>
<td>0.51 (95% CI: 0.22-1.15)</td>
<td></td>
</tr>
<tr>
<td>mPFS (months)*</td>
<td>7.7</td>
<td>7.2</td>
<td>5.5</td>
<td>8.6</td>
</tr>
<tr>
<td>p value</td>
<td>p=0.016</td>
<td></td>
<td>p=0.0192</td>
<td></td>
</tr>
<tr>
<td>hazard ratio</td>
<td>0.57</td>
<td></td>
<td>1.83</td>
<td></td>
</tr>
</tbody>
</table>

*Confidence intervals for mPFS were not provided in the presentation slides.*
In the CAIRO2 study, Tol and colleagues analyzed tumor samples from 528 of 755 previously untreated patients with metastatic colorectal cancer who were randomly assigned to receive capecitabine, oxaliplatin and bevacizumab (CB regimen n=378) or the same regimen plus C (CBC regimen n=377). A KRAS mutation was found in 40% of tumors (108 from patients in the CB group and 98 from the CBC group). Patients with KRAS mutations treated with C had significantly shorter PFS than the KRAS WT patients who received C (8.1 vs. 10.5 months, respectively, p=0.04). In addition, patients who had MT KRAS tumors who received C had significantly shorter PFS than patients with MT KRAS tumors who did not receive C (8.1 vs. 12.5 months, respectively, p=0.003) and overall survival (OS) (17.2 versus 24.9 months, respectively, p=0.03). For patients with WT tumors, there were no significant PFS differences between the 2 groups. Overall, patients treated with C who had tumors with a mutated KRAS gene had significantly decreased PFS as compared with C-treated patients with WT KRAS tumors or patients with mutated KRAS tumors in the CB group.

Karapetis and colleagues analyzed tumor samples from 394 of 572 patients (69%) with colorectal cancer who were randomly assigned to receive C plus BSC (n=287) versus BSC alone (n=285) for KRAS mutations and assessed whether mutation status was associated with survival. The patients had advanced colorectal cancer, had failed chemotherapy and had no other standard anticancer therapy available. Of the tumors that were evaluated (198 from the C group and 196 from the BSC group), 41% and 42% had a KRAS mutation, respectively. In patients with WT KRAS tumors, treatment with C as compared to best supportive care alone improved OS (median, 9.5 months versus 4.8 months, respectively; hazard ratio [HR] for death 0.55; 95% CI: 0.41-0.74; p=0.001) and PFS (median, 3.7 months versus 1.9 months, respectively; HR for progression to death, 0.98; 95% CI: 0.80 to 1.21; p=0.001). For patients with MT KRAS tumors, there were no significant differences between those treated with C versus BSC alone with respect to OS (HR, 0.98; p=0.89) or PFS (HR, 0.99; p=0.96).

Douillard and colleagues reported the results of a multicenter, Phase III trial, in which patients with no prior chemotherapy for metastatic colorectal cancer (mCRC), ECOG performance status of 0 to 2, and available tissue for biomarker testing were randomly assigned 1:1 to receive panitumumab-FOLFOX4 versus FOLFOX4. The primary endpoint was PFS; OS was a secondary endpoint. Results were prospectively analyzed on an intent-to-treat basis by tumor KRAS status. KRAS results were available for 93% of the 1,183 patients randomly assigned. In the WT KRAS group panitumumab-FOLFOX4 significantly improved PFS compared with FOLFOX4 alone (median PFS, 9.6 vs. 8.0 months, respectively; HR: 0.80; 95% CI: 0.66 to 0.97; p=0.02). A nonsignificant increase in OS was also observed for panitumumab-FOLFOX4 versus FOLFOX4 (median OS: 23.9 vs. 19.7 months, respectively; HR: 0.83; 95% CI: 0.67 to 1.02; p=0.072). In the mutant KRAS group, PFS was significantly reduced in the panitumumab-FOLFOX4 arm versus the FOLFOX4 arm (HR: 1.29; 95% CI: 1.04 to 1.62; p=0.02), and median OS was 15.5 months versus 19.3 months, respectively (HR: 1.24; 95% CI: 0.98 to 1.57; p=0.068). Adverse event rates were generally comparable across arms with the exception of toxicities known to be associated with anti-EGFR therapy. The study demonstrated that panitumumab-FOLFOX4 was well-tolerated and significantly improved PFS in patients with WT KRAS tumors.
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The CRYSTAL trial demonstrated that the addition of cetuximab to a combined first-line chemotherapy regimen of irinotecan, infusional fluorouracil and leucovorin (FOLFIRI) statistically significantly reduced the risk of disease progression and increased the chance of response in patients with metastatic colorectal cancer that was KRAS wild-type, compared with chemotherapy alone. An updated analysis of the CRYSTAL trial reported increased follow-up time and an increased number of patients evaluable for tumor KRAS status and considered the clinical significance of the tumor mutation status of BRAF in the expanded population of patients with KRAS wild-type tumors. Subsequent to the initial published analysis, which had a cutoff for OS of December 2007, and an associated overall median duration of follow-up of 29.7 months, additional tumor analysis allowed for the typing of an additional 523 tumors for KRAS mutation status, representing an increase in the ascertainment rate from 45% of intent to treat population patients in the original analysis to 89% (540 to 1,063) in the current analysis, with mutations detected in 37% of tumors. The updated analysis of OS was carried out with a new cutoff date of May 2009, giving an overall median duration of follow-up of 46 months. The addition of cetuximab to FOLFIRI in patients with KRAS wild-type disease resulted in significant improvements in OS (median, 23.5 vs. 20.0 months; HR: 0.796; p=0.0093), PFS (median, 9.9 vs. 8.4 months; HR: 0.696; p=0.0012), and response (rate 57.3% vs. 39.7%; odds ratio: 2.069; p<0.001) compared with FOLFIRI alone. Significant interactions between KRAS status and treatment effect were noted for all key efficacy endpoints. KRAS mutation status was confirmed as a powerful predictive biomarker for the efficacy of cetuximab plus FOLFIRI. BRAF V600E mutations were detected in 60 (6%) of 999 tumor samples evaluable for both BRAF and KRAS. In all but one case, BRAF mutations were identified in tumors which were wild type for KRAS. The impact of BRAF tumor mutation status in relation to the efficacy of cetuximab plus FOLFIRI was examined in the population of patients with KRAS wild-type disease (n=625). There was no evidence of an independent treatment interaction by tumor BRAF mutation status. The authors concluded that BRAF mutation status was not predictive of treatment effects of cetuximab plus FOLFIRI but that BRAF tumor mutation was a strong indicator of poor prognosis for all efficacy endpoints compared with those whose tumors were WT.

Peeters and colleagues reported the results of a Phase III study in which 1,186 patients with metastatic CRC were randomized to receive panitumumab with FOLFIRI versus FORFIRI alone as second-line treatment. The study endpoints were PFS and OS, which were independently tested and prospectively analyzed by KRAS status. KRAS status was available for 91% of patients: 597 (55%) with WT KRAS tumors, and 486 (45%) with MT KRAS tumors. In the WT KRAS subpopulation, when panitumumab was added to chemotherapy, a significant improvement in PFS was observed (HR: 0.73; 95% CI: 0.59 to 0.90; p=0.004); median PFS was 5.9 months for panitumumab-FOLFIRI versus 3.9 months for FOLFIRI. A nonsignificant trend toward increased OS was observed; median OS was 14.5 months versus 12.5 months, respectively (HR: 0.85, 95% CI: 0.70 to 1.04; p=0.12); response rate was improved to 35% versus 10% with the addition of panitumumab. In patients with MT KRAS, there was no difference in efficacy. Adverse events were comparable across arms. The authors concluded that panitumumab plus FOLFIRI significantly improved PFS and is well-tolerated as second-line treatment in patients with WT KRAS mCRC.

Maughan and colleagues reported the results of a Phase III, multicenter trial (MRC COIN trial) which randomized patients with advanced colorectal cancer who had not received previous chemotherapy to oxaliplatin and fluoropyrimidine chemotherapy (arm A) or the same combination plus cetuximab. The comparison between arms A and B (for which the primary outcome was OS) was in patients with KRAS
wild-type tumors. Baseline characteristics were well balanced between the trial groups. Analysis was by intention to treat and treatment allocation was not masked. Further analysis with respect to other mutations, including BRAF, was done. 1,630 patients were randomly assigned to treatment groups (n=815 to standard therapy and 815 to the addition of cetuximab). Tumor samples from 1,316 (81%) of patients were used for somatic mutation analyses; 43% had KRAS mutations. In patients with KRAS wild-type tumors, OS did not differ between treatment groups (median survival, 17.9 months in the control group versus 17.0 months in the cetuximab group (HR: 1.04, 95% CI: 0.87-1.23, p=0.67). BRAF mutations were detected in 8% of patients; wild-type BRAF did not show any evidence of a benefit from the addition of cetuximab. Contrary to other trials that have assessed KRAS mutation status and the benefit of the addition of cetuximab to the regimen of wild-type KRAS patients, this trial did not show a benefit of the addition of cetuximab to oxaliplatin-based chemotherapy.

**Systematic Reviews**

Qiu and colleagues conducted a meta-analysis of 22 studies on the predictive and prognostic value of KRAS mutations in mCRC patients treated with cetuximab. The overall KRAS mutation rate was 38% (829 of 2,188 patients). The results of the meta-analysis were consistent with previous reports on the use of cetuximab and KRAS mutation status, that patients with tumors that harbor mutant-type KRAS are more likely to have a worse response, PFS and OS when treated with cetuximab when compared to those with wild type KRAS.

Dahabreh and colleagues conducted a systematic review of randomized, controlled trials that assessed the use of KRAS mutation testing as a predictive biomarker for treatment of advanced colorectal cancer with cetuximab and panitumumab. The authors concluded that, compared to patients with wild type KRAS, KRAS mutations are consistently associated with reduced OS and PFS and increased treatment failure rates among patients with advanced colorectal cancer who are treated with anti-EGFR antibodies.

A pooled analysis of the CRYSTAL and OPUS randomized clinical trial data was performed to further investigate the findings of these trials in patients with KRAS wild-type tumors, using extended survival data and following an enhancement in the ascertainment rate of KRAS and BRAF tumor mutation status. Pooled individual patient data from each study were analyzed for OS, PFS and best objective response rate (ORR) in patients evaluable for KRAS and BRAF mutation status. Treatment arms were compared according to mutation status using log-rank and Cochran-Mantel-Haenszel tests. In 845 patients with KRAS wild-type tumors, adding cetuximab to chemotherapy led to a significant improvement in OS (HR: 0.81; p=0.0062), PFS (HR: 0.66; p<0.001), and ORR (odds ratio: 2.16; p<0.0001). BRAF mutations were detected in 70 of 800 (8.8%) evaluable tumors. No significant differences were found in outcome between the treatment groups in these patients. However, prognosis was worse in each treatment arm for patients with BRAF tumor mutations compared with those with BRAF wild-type tumors. This analysis of pooled data from the CRYSTAL and OPUS studies confirms the consistency of the benefit obtained across all efficacy endpoints from adding cetuximab to first-line chemotherapy in patients with KRAS wild-type mCRC. It further suggests that BRAF mutation does not appear to be a predictive biomarker in this setting, but is a marker of poor prognosis.
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Single-Arm Studies (Cetuximab or Panitumumab)
In addition to the three randomized trials outlined here, several single-arm studies that retrospectively evaluated KRAS mutational status and treatment response, showed similar nonresponse to anti-EGFR monoclonal antibodies in patients with MT KRAS tumors in metastatic colorectal cancer. These studies are summarized in Table 4.

Table 4. Single-Arm Studies Showing Objective Response Rate (n [%]) to Anti-EGFR Monoclonal Antibodies in Chemotherapy Refractory Metastatic Colorectal Cancer

<table>
<thead>
<tr>
<th>Study</th>
<th>Treatment</th>
<th>Total patients (WT:MT)</th>
<th>WT n (%)</th>
<th>MT n (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lievre et al. 2008</td>
<td>C +/- CT</td>
<td>89 (65:24)</td>
<td>34 (44)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>De Roock et al. 2008</td>
<td>C +/- CT</td>
<td>113 (57:46)</td>
<td>27 (41)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Khambata-Ford et al. 2007</td>
<td>C</td>
<td>80 (50:30)</td>
<td>5 (10)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Di Fiore et al. 2007</td>
<td>C + CT</td>
<td>59 (43:16)</td>
<td>13 (28)</td>
<td>0 (0)</td>
</tr>
<tr>
<td>Benvenuti et al. 2007</td>
<td>P or C or C + CT</td>
<td>48 (32:16)</td>
<td>10 (31)</td>
<td>1 (6)</td>
</tr>
</tbody>
</table>

C: cetuximab; CT: chemotherapy; P: panitumumab; WT: wild type; MT: mutated

Two of these single-arm studies also reported a difference in PFS and OS, as summarized in Table 5.

Table 5. Single-Arm Studies of Treatment of Metastatic Colorectal Cancer with Anti-EGFR Monoclonal Antibodies and KRAS Mutational Status

<table>
<thead>
<tr>
<th>Study/Year</th>
<th>Description</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>De Roock et al. 2008</td>
<td>113 patients with irinotecan (I) -refractory mCRC treated with cetuximab (C) with or without I</td>
<td>Overall response (n=108), C+I and C 27/66 (41%) 0/42 (0%) p=0.000001 (C+I) p=0.126 (C alone) mPFS (C+I) 34 weeks (95% CI: 28.5–40.0) 12 weeks (95% CI: 5.4–18.7) p=0.016 mPFS (C) 12 weeks (95% CI: 4.2–20.0) 12 weeks (95% CI: 7.0–17.0) p=0.351</td>
</tr>
</tbody>
</table>
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<table>
<thead>
<tr>
<th>Lievre et al. 2008</th>
<th>89 patients treated with C monotherapy after treatment failure with I</th>
</tr>
</thead>
<tbody>
<tr>
<td>WT:MT:</td>
<td>65 (73%):24 (27%)</td>
</tr>
<tr>
<td>Response rate</td>
<td>40%</td>
</tr>
<tr>
<td>0%</td>
<td>p&lt;0.001</td>
</tr>
<tr>
<td>mPFS</td>
<td>31.4 weeks (95% CI: 19.4–36)</td>
</tr>
<tr>
<td>10.1 weeks (95% CI: 8–16)</td>
<td>p=0.0001</td>
</tr>
<tr>
<td>mOS</td>
<td>14.3 months (95% CI: 9.4–20)</td>
</tr>
<tr>
<td>10.1 months (95% CI: 5.1–13)</td>
<td>p=0.026</td>
</tr>
</tbody>
</table>

C: cetuximab; I: irinotecan; mCRC: metastatic colorectal cancer; WT: wild type; MT=mutated; mPFS: median progression-free survival; mOS: median overall survival

**BRAF**

A meta-analysis of BRAF mutation and resistance to anti-EGFR monoclonal antibodies in patients with metastatic colorectal cancer was performed. The primary endpoint of eligible studies was ORR, defined as the sum of complete and partial tumor response (CR and PR). There were a total of 11 studies, with sample sizes ranging from 31 to 259 patients. All studies were conducted retrospectively (one study was a nonconcurrent analysis of response in a population previously randomized). Anti-EGFR therapy was given as first-line treatment in one study and as second-line or greater in the other 10. In 2 studies, the anti-EGFR monoclonal antibody was given as monotherapy, and in 9 studies, patients received various chemotherapies. Seven studies were performed in unselected patients (i.e., KRAS mutational status was unknown) totaling 546 patients, for whom 520 were assessable for tumor response. In the unselected population, a BRAF mutation was detected in 8.8% of patients, and the ORR for patients with mutant BRAF was 29.2% (14/48) and for WT BRAF was 33.5% (158/472; p=0.048). Four studies were performed in patients with WT KRAS metastatic colorectal cancer. BRAF mutational status was performed on 376 KRAS WT tumors. BRAF mutation was detected in 10.6% (n=40) of primary tumors. Among the 376 analyzed, all patients were assessable for tumor response. ORR of patients with mutant BRAF was 0% (0 of 40), whereas the ORR of patients with WT BRAF was 36.3% (122 of 336). Only 3 studies presented data on PFS and OS; and therefore, a pooled analysis was not performed. The authors conclude that although the meta-analysis provided evidence that BRAF mutation is associated with lack of response to anti-EGFR monoclonal antibodies in WT KRAS metastatic colorectal cancer, the number of studies and number of patients included in the meta-analysis were relatively small and that large studies are needed to confirm the results of the meta-analysis using homogenous metastatic colorectal cancer patients with assessors blinded to the clinical data.
Phillips and colleagues analyzed the data from 4 studies which reported tumor response and survival in patients with mCRC treated with anti-EGFR monoclonal antibodies as related to BRAF mutational status. Di Nicolantonio and colleagues looked retrospectively at 113 patients with mCRC who had received cetuximab or panitumumab. None of the BRAF-mutated tumors responded to treatment (0 of 11), whereas 32.4% (22 of 68) of the BRAF WT did. Loupakis and colleagues retrospectively assessed 87 patients receiving I and C. Of the 87 patients in the study, BRAF was mutated in 13 cases, and none of them responded to chemotherapy, compared to 32% (24 of 74) with WT BRAF who did. In the CAIRO2 study, a retrospective analysis of BRAF mutations was performed in 516 available tumors from patients previously randomized to CB regimen or the same regimen plus cetuximab (CBC regimen). A BRAF mutation was found in 8.7% (n=45) of the tumors. Patients with a BRAF mutation had a shorter median PFS and OS compared to WT BRAF tumors in both treatment arms. The authors concluded that a BRAF mutation is a negative prognostic marker in patients with mCRC and that this effect, in contrast to KRAS mutations, is not restricted to the outcome of cetuximab treatment. In the CRYSTAL trial, Van Cutsem and colleagues randomized 1,198 patients with untreated mCRC to FOLFIRI with or without cetuximab. A recent analysis of BRAF mutations in this patient population and the influence on outcome was presented at the 2010 American Society of Clinical Oncology (ASCO) Gastrointestinal Cancers Symposium. The authors showed that of the KRAS WT/BRAF-mutated patients, the OS for FOLFIRI plus cetuximab and FOLFIRI alone was 14.1 and 10.3 months, respectively (p=0.744). Although this was not statistically significant, it showed a trend toward improved OS, PFS, and response, suggesting that KRAS wild-type/BRAF-mutant patients may benefit from anti-EGFR therapy. This unpublished analysis is the first to show a possible benefit of anti-EGFR therapy in patients with BRAF-mutant tumors.

De Roock and colleagues reported the effects of 4 mutations, including BRAF, on the efficacy of cetuximab and chemotherapy in chemotherapy-refractory metastatic colorectal cancer in 773 primary tumor samples. Tumor samples were from fresh frozen or FFPE tissue, and the mutation status was compared to retrospectively collected clinical outcomes including objective response, PFS, and OS. BRAF mutations were found in 36 of 761 tumors (4.7%). In patients with WT KRAS, carriers of BRAF mutations had a significantly lower response rate (8.3% or 2 of 24 patients) than BRAF WT (38.0% or 124 of 326 patients; odds ratio [OR]: 0.15; 95% CI: 0.02-0.51; p=0.0012). PFS for BRAF-mutated versus WT was a median of 8 weeks versus 26 weeks, respectively (HR: 3.74; 95% CI: 2.44-5.75; p<0.0001) and OS median 26 weeks versus 54 weeks, respectively (HR: 3.03; 1.98-4.63; p<0.0001).

Mao and colleagues conducted a meta-analysis of BRAF mutation V600E and resistance to anti-EGFR monoclonal antibodies in patients with metastatic colorectal cancer. Eleven studies were included, with sample sizes ranging from 31 to 259; all of the studies were retrospective analyses. Seven of the studies included unselected patients, and 4 included only patients with wild-type KRAS. The primary endpoint was ORR. In the 7 studies with unselected patients, BRAF mutational status was performed successfully on 546 mCRC. BRAF mutation was detected in 8.8% of primary tumors. The ORR of mCRC patients with mCRC with mutant BRAF was 29.2% versus 33.5% in patients with wild-type BRAF. In the 4 studies that included patients with wild-type KRAS, BRAF mutational status was performed successfully on 376 KRAS wild-type mCRC. BRAF mutations were detected in 10.6% of primary tumors. The ORR of patients with mutant BRAF was 0.0%, whereas the ORR of patients with wild-type BRAF was 36.3%. The authors concluded that the
results of their meta-analysis provided evidence that BRAF mutation is associated with lack of response in wild-type KRAS mCRC treated with anti-EGFR monoclonal antibodies.

An updated analysis of the CRYSTAL trial reported increased follow-up time and an increased number of patients evaluable for tumor KRAS status and considered the clinical significance of the tumor mutation status of BRAF in the expanded population of patients with KRAS wild-type tumors. The impact of BRAF tumor mutation status in relation to the efficacy of cetuximab plus FOLFIRI was examined in the population of patients with KRAS wild-type disease (n=625). There was no evidence of an independent treatment interaction by tumor BRAF mutation status. The authors concluded that BRAF mutation status was not predictive of treatment effects of cetuximab plus FOLFIRI but that BRAF tumor mutation was a strong indicator of poor prognosis for all efficacy endpoints compared with those whose tumors were WT.

At the latest review of this policy (December 2012), no additional clinical trials were identified on the clinical use of BRAF mutation analysis to guide anti-EGFR therapy in patients with metastatic CRC.

Summary
In summary, clinical trial data show that patients with KRAS-mutated metastatic colorectal cancer do not benefit from cetuximab or panitumumab, either as monotherapy or in combination with other treatment regimens. These data support the use of KRAS mutation analysis of tumor DNA before considering use of cetuximab or panitumumab in a treatment regimen. Identifying patients whose tumors express mutated KRAS will avoid exposing patients to ineffective drugs and unnecessary drug toxicities and expedites the use of alternative therapies. Thus, KRAS mutation analysis may be considered medically necessary to predict nonresponse to anti-EGFR monoclonal antibodies in the treatment of metastatic colorectal cancer.

The data for patients with metastatic colorectal cancer and a BRAF mutation have shown consistently that a BRAF mutation is a poor prognostic marker, as it is associated with shorter PFS and OS, regardless of treatment. Most of the data for a BRAF mutation predicting response to anti-EGFR therapy are limited by small numbers of patients and conflicting results among studies. The large, randomized CRYSTAL trial, with nonconcurrent subgroup analyses of BRAF mutations in patients previously randomized, reported the impact of BRAF tumor mutation status in relation to the efficacy of cetuximab plus FOLFIRI in the population of patients with KRAS wild-type disease. There was no evidence of an independent treatment interaction by tumor BRAF mutation status, and the trial showed that BRAF mutation status was not predictive of treatment effects of cetuximab plus folinic acid [leucovorin], 5-FU, and irinotecan (FOLFIRI). BRAF tumor mutation was a strong indicator of poor prognosis for all efficacy endpoints compared with those whose tumors were BRAF WT. Thus, BRAF mutation analysis is considered investigational to predict nonresponse to anti-EGFR monoclonal antibodies in the treatment of metastatic colorectal cancer.

References
KRAS and BRAF Mutation Analysis in Metastatic Colorectal Cancer

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Policy History
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12/03/2008 Medical Director review
12/04/2008 Medical Director review
12/16/2008 Medical Policy Committee approval. No change to coverage.
12/01/2010 Medical Policy Committee review
12/15/2010 Medical Policy Implementation Committee approval. No change to coverage.
12/08/2011 Medical Policy Committee review
12/21/2011 Medical Policy Implementation Committee approval. Title changed to indicate inclusion of BRAF testing to the policy. BRAF testing policy statement added as investigational to predict nonresponse to anti-EGFR monoclonal antibodies cetuximab and panitumumab in the treatment of metastatic colorectal cancer.
12/06/2012 Medical Policy Committee review
12/19/2012 Medical Policy Implementation Committee approval. No change to coverage.
03/04/2013 Coding revised
12/12/2013 Medical Policy Committee review
12/18/2013 Medical Policy Implementation Committee approval. No change to coverage.

Next Scheduled Review Date: 12/2014

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